Stereoselective Synthesis of (±)-Ancistrofuran and its Stereoisomers

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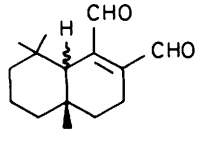
The four possible stereoisomers of ancistrofuran have been prepared from γ-cyclohomocitral. Addition of 3-furyl-lithium yielded two epimeric alcohols. Each alcohol was epoxidised with *m*-chloroperbenzoic acid and reduction with lithium aluminium hydride gave mixtures of two diols in each case. Treatment of each mixture with toluene-p-sulphonyl chloride gave the four stereoisomers of ancistrofuran. A stereoselective synthesis was also developed to the *trans*-fused ancistrofuran which was identical with the natural isomer. Lactol (**22**) was conveniently prepared by di-isobutyl aluminium hydride reduction of lactone (**23**). Reaction of the lactol with 2 mol equiv. of 3-furyl-lithium gave a mixture of two diols in 3:1 ratio. Oxidation with manganese dioxide gave ketone (**24**) which underwent reduction with lithium triethylborohydride in a highly stereoselective manner to yield diol (**13**). Ketone (**24**) was also prepared in one step by reaction of lactone (**23**) with 1 mol equiv. of 3-furyl-lithium. Subsequent treatment of diol (**13**) with toluene-*p*-sulphonyl chloride gave ancistrofuran, identical with the natural product. The stereoselective reduction of the γ-hydroxy ketone has been discussed and is suggested to involve 'chelation control'.

A variety of different compounds, many of them terpenoid, have been identified as components of the defence secretion of termites.[1] These compounds range from relatively simple derivatives such as benzoquinone and toluquinone,[2] (*E*)-1-nitropentadec-2-ene,[3] tetradec-1-en-3-one, hexadec-1-en-3-one, tridecan-2-one, and β-keto-aldehydes[4] found in the Rhinotermitidae family to the chemically more interesting and diverse diterpenoid[1,5] and macrolide[5,6] derivatives found in the Nasutitermitinae and Armitermes, respectively. Many termites utilise mixtures of monoterpenes[2,7] in their defence and these are frequently accompanied by sesquiterpene[7] or diterpene[8] hydrocarbons. Oxygenated sesquiterpene derivatives have also been isolated from some termites and the frontal gland of soldiers of the West African termites *Amitermes evuncifer* contains a secretion which is composed of >90% of a sesquiterpene ether, 4,11-epoxy-*cis*-eudesmane.[9] The minor components consisted of 10-*epi*-eudesma-3,11-diene, 8-*epi*-caparrapi oxide, caparrapi oxide, and *cis*-β-ocimene.[10] The major component of the secretion of *Armitermes excellens* has been demonstrated to be a sesquiterpene alcohol, amiteol, a eudesmane derivative with a 7β,10β-skeleton.[11]

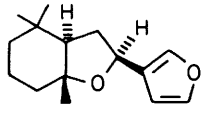
The soldiers of the macrotermitinae species *Ancistrotermes cavithorax* are dimorphic and it was interesting to find that the secretion in each caste is different.[12] The major soldiers produce a mixture of four components, α- and β-cyclogeraniolene together with two novel sesquiterpenes, cavidial (**1**) and ancistrofuran (**2**). In contrast the minor soldiers produce ancistrodial (**3**) which constitutes *ca.* 90% of the volatile secretion. A synthesis of ancistrodial has previously been reported[12] but the structure of cavidial (**1**) has still to be confirmed. Although two syntheses of (±)-ancistrofuran have been reported[13,14] neither route was stereoselective and both involved difficult separations of undesired isomers. We now report on an efficient and stereoselective synthesis of ancistrofuran together with a remarkably stereoselective reduction of an α-hydroxy ketone. The four possible stereoisomers of ancistrofuran have also been prepared from a common intermediate.

Results and Discussion

(1) *Synthesis of Ancistrofuran* (2) *and its Stereoisomers.*—The first approach taken allowed the preparation of all four stereoisomers from a common intermediate. The starting point for the synthesis was γ-cyclohomocitral (**4**), which was readily available *via* Claisen rearrangement of the allyl vinyl ether (**5**).[15] Heating the allyl vinyl ether (**5**) at 190 °C for 90 min gave γ-cyclohomocitral in 95% yield. Subsequent steps involved addition of 3-furyl-lithium, hydration of the exocyclic olefin, and a cyclisation procedure to form the tetrahydrofuran ring. Thus, addition of γ-cyclohomocitral (**4**) to a solution of 3-furyl-lithium at −78 °C yielded the epimeric alcohols (**6**) and (**7**) in the ratio 3:2 in 79% yield, which were easily separable by flash chromatography, and the structures were assigned on the basis



(**1**)



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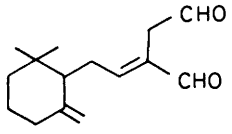
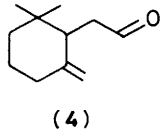
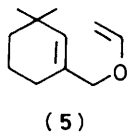


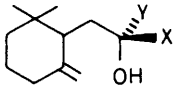
(**3**)



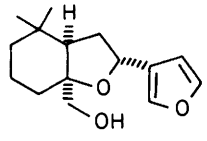
(**4**)



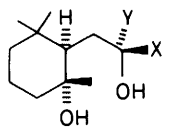
(**5**)



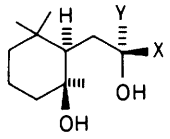
(**6**) X = 3-Furyl, Y = H
(**7**) X = H, Y = 3-Furyl



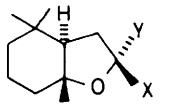
(**8**)



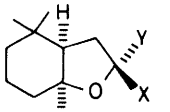
(9) X = 3-Furyl, Y = H
(13) X = H, Y = 3-Furyl



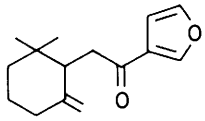
(10) X = 3-Furyl, Y = H
(14) X = H, Y = 3-Furyl



(11) X = H, Y = 3-Furyl
(2) X = 3-Furyl, Y = H



(12) X = H, Y = 3-Furyl
(15) X = 3-Furyl, Y = H



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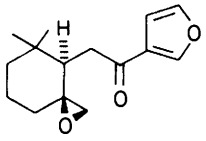
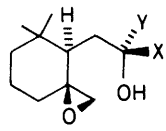
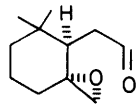


(17)



(18) X = H, Y = 3-Furyl
(19) X = 3-Furyl, Y = H



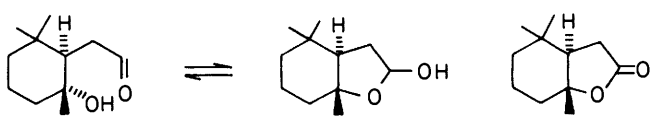
(20)

of spectral characteristics and by comparison with data obtained from model studies.* Further information on the stereochemistry was obtained by subsequent conversion into the final cyclic ethers. Treatment of the alcohol (**6**) with *m*-chloroperbenzoic acid (MCPBA) in methylene dichloride gave a complex mixture of products from which the cyclic ether (**8**), assigned on the basis of spectral characteristics, was isolated as the major component. Treatment of the crude reaction mixture with lithium aluminium hydride, however, did allow the isolation of two diols (**9**) and (**10**) albeit in low yield. Each of these diols on treatment with toluene-*p*-sulphonyl chloride in pyridine underwent cyclisation to yield the required cyclic ethers (**11**) and (**12**).

In an analogous series of reactions the epimeric alcohol (**7**) was transformed into the corresponding cyclic ethers (**2**) and (**15**) *via* the diols (**13**) and (**14**). All attempts to improve the yield of the epoxidation reaction were unsuccessful since it appeared that the reactivity of the furan ring towards electrophilic reagents surpassed that of the exocyclic olefinic moiety. In addition, formation of the bicyclic ether remained a problem. In an attempt to avoid both these problems it was considered that oxidation to the ketone (**16**) would both prevent cyclisation to the ether (**8**) and serve to deactivate the furan ring towards electrophilic reagents. Manganese dioxide oxidation of the mixture of epimeric alcohols gave, as a single crystalline product, the ketone (**16**). Reaction of this ketone with MCPBA gave a *single* product, which was identified as the epoxide (**17**). The stereochemistry was confirmed by its subsequent conversion into the *cis*-fused cyclic ethers (**12**) and (**15**).

To complete the synthesis all that remained was reduction of the epoxide and ketone functionalities, followed by cyclisation. Lithium aluminium hydride reduction at 0 °C in diethyl ether gave a 3:1 mixture of the epimeric alcohols (**18**) and (**19**) in a combined yield of 69%; the two epimers were separated by flash chromatography. Treatment of each of these epoxy-alcohols with lithium aluminium hydride in tetrahydrofuran (THF) at reflux gave the corresponding diols (**10**) and (**14**) in good yield. Cyclisation then gave the ethers (**12**) and (**15**). Formation of the *cis*-fused ethers (**12**) and (**15**) can only be due to the stereochemical outcome of the epoxidation reaction. Delivery of the oxygen atom to the olefin (**16**) to give (**17**) must have occurred on the more stereically hindered face. Indeed, treatment of this olefin (**16**) with iodine–silver(I) oxide, a reagent that is known to be sensitive to steric control,[16] gave a single product identical with the peracid oxidation product. This was confirmed by its transformation into the cyclic ethers (**12**) and (**15**). Whilst the observed stereoselectivity of the iodine–silver(I) oxide is that predicted, the outcome of the peracid oxidation is not. The origin of the exclusive formation of compound (**17**) is not readily apparent but might result from hydrogen-bond interaction of the reagent to the carbonyl oxygen which might direct the attacking species from one side of the molecule.† An alternative reduction of the epoxyketone (**17**) using lithium triethylborohydride at −50 °C gave a 72% yield of the epoxy alcohols (**18**) and (**19**) in the ratio 1:2.5. This is the reverse stereoselectivity to that observed in the lithium aluminium hydride reduction. The combination of these complementary reductions, together with the completely stereoselective epoxidation of enone (**16**), give moderately stereoselective routes to the *cis*-fused ancistrofurans (**12**) and (**15**).

(2) *Stereoselective Synthesis of Ancistrofuran.*—We now turned our attention to the development of a stereoselective route to the *trans*-fused ancistrofurans and in particular the natural isomer (**2**). Our work on the stereoselective reduction of the ketone (**17**) led us to speculate that stereoselective reaction of the aldehyde (**20**) with 3-furyl-lithium might be anticipated. However, all attempts to prepare the required aldehyde (**20**) were unsuccessful. As an alternative we decided to investigate the reaction of 3-furyl-lithium with the aldehyde (**21**) which will exist in equilibrium with the lactol (**22**). The lactol (**22**) is most conveniently prepared by di-isobutyl aluminium hydride reduction of the lactone (**23**) which is available *via* the mercuric-initiated electrophilic cyclisation of homogeranic acid.[17] Reaction of the lactol (**22**) with 2 mol equiv. of 3-furyl-lithium



(21) (22) (23)

* P. Briner, Ph.D. Thesis, Southampton, 1978.
† We acknowledge a referee's suggestion.

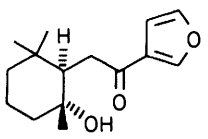
Table. Reduction of γ-hydroxy ketone (**24**)

Reducing agent	Products[a] (**13**)	(**9**)	Yield (%)[b]
$LiAlH_4$	40	60	80
$NaBH_4$	50	50	84
$ZnBH_4$	60	40	66
$LiBEt_3H$	100	0	88

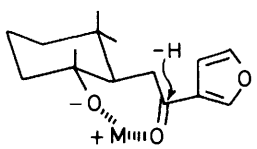
[a] Ratio of products measured by g.l.c. (3 m × 3 mm; 5% OV101 at 190 °C). [b] Refers to isolated yield.

gave a mixture of diols (**9**) and (**13**) in 75% yield. The stereoselectivity of this reaction proved to be variable, giving at best a 3:1 mixture of (**9**) and (**13**), the major product being the undesired diol, and at worst the reaction proved to be non-stereoselective. In addition all attempts to separate these components by flash chromatography were unsuccessful.

Our attention was now turned to the reduction of the ketone (**24**) and by analogy with the reduction of the epoxy ketone (**17**) it was anticipated that stereoselective reduction of the carbonyl might be possible. The mixture of diols (**9**) and (**13**) was treated with manganese dioxide in methylene dichloride to yield the required ketone (**24**) in 90% yield. This ketone could also be prepared in one step by reaction of the lactone (**23**) with 1 mol equiv. of 3-furyl-lithium. The possible stereoselective reduction of ketone (**24**) was then investigated. Reduction with lithium aluminium hydride, zinc borohydride, and sodium borohydride all yielded mixtures of diols (**9**) and (**13**) (Table). However, reduction with 2 mol equiv. of lithium triethylborohydride in THF proceeded in a highly stereoselective manner to yield the required diol (**13**) as the only product in 88% yield as a white crystalline solid, m.p. 85—87 °C. Treatment of the diol with 1 mol equiv. of toluene-*p*-sulphonyl chloride and 2 mol equiv. of pyridine in methylene dichloride gave a quantitative yield of ancistrofuran (**2**).



(**24**)



(**25**)

This appears to be the first example of stereoselective reduction of a γ-hydroxy ketone. The basis of this remarkably high degree of stereoselectivity in the reduction could involve initial chelation of the reducing agent involving a metal atom and the hydroxy and carbonyl groups as shown in structure (**25**). Whilst the existence of partial bonds would require to be invoked for chelation of boron, and this has previously been suggested,[18] it would appear more likely that the two oxygen atoms are involved in co-ordination to the lithium atom. Attack of hydride from a second equivalent of reducing agent can now only occur from the less hindered β-face. Stereoselective reduction of α- and β-hydroxy ketones has also been reported and the high *erythro*-selectivity found with zinc borohydride was attributed to metal chelation in the transition state.[19] Kishi and co-workers[20] have developed conditions for the reduction of γ- and δ-epoxy ketones and a high degree of stereoselectivity was found with a combination of lithium aluminium hydride and 2-(*o*-toluidinomethyl)pyrrolidine. The use of 'chelation control' in the reaction of Grignards[21] and cuprates[22] also clearly demonstrates the importance of chelation-controlled transition states. The present work would appear to demonstrate the first example of stereocontrol in reduction of a γ-hydroxy ketone.

Experimental

I.r. spectra were recorded on a Perkin-Elmer 157G spectrophotometer and ^1H n.m.r. spectra on a Varian XL-100 (100 MHz) or a Hitachi-Perkin-Elmer R-24B (60 MHz) instrument using $CDCl_3$ as solvent. Mass spectra were measured on a Kratos MS 30 spectrometer using electron impact (e.i.) or chemical ionisation modes. T.l.c. was carried out using pre-coated silica gel plates [Merck Kieselgel 60F (255)], and flash chromatography[23] on silica gel 60 (230—400 mesh; Macherey–Nagal). All solvents were dried and distilled before use. Ether refers to diethyl ether and light petroleum refers to the fraction boiling between 40—60 °C.

2,2-Dimethyl-6-methylenecyclohexaneacetaldehyde (*γ-Cyclohomocitral*) (**4**).—A Carius tube which had been washed with 10% aqueous sodium hydroxide and thoroughly dried was charged with the allyl vinyl ether (**5**)[15] (5.0 g) and sealed *in vacuo*. The tube was heated at 190 °C for 90 min to effect rearrangement. The crude product was purified by flash chromatography [ether–light petroleum (4:96)] to yield an oil (4.9 g, 95%) having identical spectral properties with those reported for γ-cyclohomocitral (**4**).[15]

(±)-(R*R*)-α-[(2,2-*Dimethyl*-6-*methylenecyclohexyl*)*methyl*]*furan*-3-*methanol* (**6**) *and* (±)-(R*S*)-α-[(2,2-*Dimethyl*-6-*methylenecyclohexyl*)*methyl*]*furan*-3-*methanol* (**7**).—To a solution of 3-bromofuran (5.0 g, 34 mmol) in THF (25 ml) at −78 °C was added n-butyl-lithium (34 mmol; 1.6M in hexane). After 15 min a solution of aldehyde (**4**) (5.0 g, 30 mmol) in THF (20 ml) was added and the mixture stirred at −78 °C for a further 15 min. The reaction was quenched by the addition of saturated aqueous ammonium chloride (10 ml) and the mixture was allowed to warm to room temperature. The mixture was extracted with ether (25 ml × 2) and the organic layers were washed with saturated aqueous sodium chloride and dried (Na_2SO_4). Removal of solvent and flash chromatography of the residue [ether–light petroleum (30:70)] afforded the less polar component (**7**) (2.3 g, 32%) followed by compound (**6**) (3.3 g, 47%) as pale yellow oils; for (**6**): $\nu_{max.}$ 3 200—3 600 (OH), 2 900, 1 455, 1 385, 1 105, and 870 cm^{-1}; δ_H (100 MHz) 0.80 and 0.85 (2 × 3H, 2 × s, 2 × CH_3), 1.2—1.8 (6H, 3 × CH_2), 2.0—2.4 (3 H, allylic H), 4.40 (1 H, m, C*H*OH), 4.60 (1 H, br s, vinylic H), 4.80 (1 H, br s, vinylic H), 6.30 (1 H, br s, furan β-H), and 7.28 (2 H, br s, furan α-H); *m/z* 234 (M^+, 17), 216 (17), 110 (100), 109 (69), 97 (89), 95 (33), 81 (18), and 60 (50); (h.r.m.s.) M^+ = 234.1610 ($C_{15}H_{22}O_2$ requires *M*, 234.1614); for (**7**): $\nu_{max.}$ 3 200—3 600 (OH), 2900, 1 455, 1 380, 1 100, and 875 cm^{-1}; δ_H (100 MHz) 0.84 and 0.96 (2 × 3 H, s, 2 × CH_3), 1.2—1.8 (6 H, 3 × CH_2), 2.0—2.4 (3 H, allylic H), 4.50 (1 H, m, C*H*OH), 4.64 (1 H, br, s, vinylic H), 4.80 (1 H, br s, vinylic H), 6.30 (1 H, br s, furan β-H), and 7.28 (2 H, br s, furan α-H); δ_C 23.7, 26.1, 28.1, 32.6, 34.6, 35.1, 36.3, 49.6, 64.6, 108.8, 109.6, 130.3, 138.5, 142.9, and 149.3 p.p.m.; *m/z* 234 (*M*, 20), 216 (25), 110 (94), 109 (70), 97 (100), 95 (35), 81 (24), and 69 (46); (h.r.m.s.) M^+ = 234.1623.

(±)-(αRS,1'SR,2'SR)-α-[(2'-*Hydroxy*-2',6',6'-*trimethylcyclohexyl*)*methyl*]*furan*-3-*methanol* (**9**) *and* (±)-(αRS, 1'SR,2'RS)-α-[(2'-*Hydroxy*-2',6',6'-*trimethylcyclohexyl*)*methyl*]*furan*-3-*methanol* (**10**).—A solution of olefin (**6**) (0.5 g, 2.1 mmol) and MCPBA (840 mg, 4.6 mmol) in methylene dichloride (50 ml) was stirred at 0 °C for 24 h. The mixture was poured into 10% aqueous sodium hydrogen carbonate (30 ml) and stirred for 30 min. The organic layer was washed with saturated aqueous sodium chloride (20 ml × 3) and dried ($MgSO_4$). Removal of

solvent gave an oily residue which was taken up in THF (10 ml) and added to a stirred suspension of lithium aluminium hydride (100 mg) in THF (30 ml) at reflux temperature. The mixture was heated under reflux for a further 30 min, then cooled to 0 °C. Water (0.5 ml) was added and the inorganic salts were filtered off and extracted with THF (10 ml × 3). The combined THF solutions were dried ($MgSO_4$) and the solvent was removed to afford a pale yellow oily residue (120 mg) which was purified by preparative reverse-phase h.p.l.c. (Dupont Zorbax 6—8 μm prepacked column), with 70% aqueous acetonitrile as eluant. There were obtained, in order of elution, the diol (**10**) (10 mg), white solid, m.p. 137—143 °C, the diol (**9**) (8 mg), white solid, m.p. 74—79 °C, and the alcohol (**8**) (89 mg), as an oil. Diols (**9**) and (**10**) were used in subsequent transformations without further purification; for (**8**): $\nu_{max.}$ 3 200—3 600, 2 855, 1 455, 1 170, 1 050, and 890 cm^{-1}; δ_H (100 MHz) 0.90 and 1.05 (6 H, 2 × s, 2 × CH_3), 1.2—1.6 (8 H), 2.0—2.2 (1 H, ring junction CH), 3.50 (2 H, s, CH_2O), 4.8 (1 H, dd, *J* 6 and 7 Hz, CHO), 6.25 (1 H, s, furan β-H), and 7.3 (2 H, s, furan α-H); *m/z* 250 (M^+, 1), 219 (100), 123 (15), 109 (23), 95 (29), and 81 (48); for (**9**): $\nu_{max.}$(CCl_4) 3 200—3 600, 1 480, 1 410, 1 180, 1 080, and 890 cm^{-1}; δ_H (100 MHz), 0.82, 0.99, and 1.26 (9 H, 3 × s, 3 × CH_3), 1.3—1.9 (9 H), 4.58 (1 H, m, C*H*OH), 6.42 (1 H, br s, furan β-H), and 7.42 (2 H, br s, furan α-H); *m/z* 252 (M^+, 1), 234 (16), 219 (14), 149 (53), 123 (41), 110 (100), 95 (63), 82 (81), 69 (87), and 55 (46); (h.r.m.s.) ($M^+ - H_2O$) = 234.1607 (Calc. for $C_{15}H_{22}O_2$: *m/z* 234.1614); for (**10**): $\nu_{max.}$ 3 200—3 600, 1 485, 1 410, 1 180, and 895 cm^{-1}; δ_H (100 MHz) 0.70, 0.98, and 1.28 (9 H, 3 × s, 3 × CH_3), 1.2—2.1 (9 H), 4.72 (1 H, m, C*H*OH), 6.46 (1 H, br s, furan β-H), and 7.40 (2 H, br s, furan α-H); *m/z* 252 (M^+, 1), 234 (10), 219 (19), 149 (60), 123 (61), 110 (90), 95 (58), 82 (100), 69 (64), and 55 (48); (h.r.m.s.) ($M^+ - H_2O$ = 234.1603.

(±)(αRS,1′RS,2′SR)-α-[(2-*Hydroxy*-2,6,6-*trimethylcyclohexyl*)*methyl*]*furan*-3-*methanol* (**14**) *and* (±)-(αRS, 1′RS, 2′RS)-α-[(2-*Hydroxy*-2,6,6-*trimethylcyclohexyl*)*methyl*]*furan*-3-*methanol* (**13**).—In a similar manner to that described above the olefin (**7**) was converted into the diols (**13**) and (**14**); compound (**13**) had m.p. 85—87 °C, $\nu_{max.}$ 3 200, 1 480, 1 405, 1 180, and 900 cm^{-1}; δ_H (100 MHz) 0.82, 0.96, and 1.24 (9 H, 3 × s, 3 × CH_3), 2.00—1.30 (9 H), 5.00 (1 H, m, C*H*OH), 6.35 (1 H, br s, furan β-H), and 7.35 (2 H, br s, furan α-H); *m/z* 234 (2), 219 (9), 123 (24), 110 (36), 97 (24), 95 (33), 69 (70), 55 (40), and 43 (100); (h.r.m.s.) ($M^+ - H_2O$) = 234.1623; compound (**14**) had m.p. 140—142 °C, $\nu_{max.}$ 3 200—3 600, 1 485, 1 405, 1 180, 1 075, and 900 cm^{-1}; δ_H (100 MHz) 0.95, 1.00, and 1.15 (9 H, 3 × s, 3 × CH_3), 1.3—2.2 (9 H), 4.8 (1 H, m, C*H*OH), 6.45 (1 H, br s, furan β-H), and 7.4 (2 H, m, furan α-H); *m/z* 252 (1), 234 (13), 219 (30), 149 (55), 123 (64), 110 (83), 82 (100), and 69 (71); (h.r.m.s.) ($M^+ - H_2O$) = 234.1603 ($C_{15}H_{22}O_2$ requires *m/z* 234.1614).

2-(2′,2′-*Dimethyl*-6′-*methylenecyclohexyl*)1-(3-*furyl*)*ethanone* (**16**).—(i) Manganese dioxide (4.35 g, 50 mmol) was added to a stirred solution of the alcohols (**6**) and (**7**) (2.34 g, 10 mmol) in methylene dichloride (100 ml). After 24 h the mixture was filtered through Celite. Removal of solvent afforded ketone (**16**) (2.1 g, 90%), m.p. 45—90 °C, which was used without further purification.

(ii) Pyridinium chlorochromate (15 mmol) supported on alumina was added to a stirred solution of the alcohols (**6**) and (**7**) (1.2 g, 5.1 mmol) in methylene dichloride (50 ml). After 3 days, hexane (100 ml) was added and the mixture filtered through Celite. Removal of solvent afforded the ketone (**16**) (1.12 g, 90%) as a white solid, m.p. 46—49 °C. Crystallisation from pentane at −20 °C afforded an *analytical sample*, m.p. 53—54 °C (Found: C, 77.4; H, 8.55. $C_5H_{20}O_2$ requires C, 77.53; H, 8.68%); $\nu_{max.}$ 3 130, 1 670 (C=O), 1 645, 1 560, 1 155, and 890 cm^{-1}; δ_H (100 MHz) 0.80 and 0.95 (6 H, 2 × s, 2 × CH_3), 1.3—1.8 (4 H, 2 × ring CH_2), 1.9—2.3 (3 H, allylic H), 2.7 (2 H, br s, CH_2CO), 4.45 (1 H, s, vinylic H), 4.65 (1 H, s, vinylic H), 6.75 (1 H, m, furan 4-H), 7.40 (1 H, m, furan 5-H), and 8.05 (1 H, m, furan 2-H); δ_C 23.7, 23.8, 28.9, 34.4, 35.1, 38.6, 38.8, 48.7, 108.6, 108.9, 128.2, 144.2, 146.9, 148.9, and 194.6 p.p.m.; *m/z* 232 (M^+, 10), 217 (5), 189 (4), 122 (25), 107 (26), 95 (100), 81 (15), and 69 (17).

2,(5′,5′-*Dimethyl*-1′-*oxaspiro*[2.5]*octan*-4′-*yl*)-1-(3-*furyl*)-*ethanone* (**17**).—(i) Olefin (**16**) (1.0 g, 4.3 mmol) and MCPBA (820 mg, 4.7 mmol) were stirred together in methylene dichloride (50 ml) for 20 h. The mixture was then poured into 5% aqueous sodium hydrogen carbonate (20 ml) and stirred for 30 min. The organic layer was washed with saturated aqueous sodium chloride (30 ml) and dried ($MgSO_4$). Removal of solvent and chromatography of the residue on silica gel with ether–hexanes (3:7) as eluant afforded the epoxide (**17**) (960 mg, 90%) as a white solid, m.p. 85—89 °C. Recrystallisation from pentane at −20 °C afforded an *analytical sample*, m.p. 91—92 °C (Found: C, 72.25; H, 8.1. $C_{15}H_{20}O_3$ requires C, 72.55; H, 8.12%).

(ii) Olefin (**16**) (100 mg, 0.43 mmol) in 1,4-dioxane (4 ml) was added to a well stirred mixture of iodine (55 mg) and silver(I) oxide (500 mg) in 80% aqueous dioxane (10 ml) in the dark. After 24 h the mixture was extracted with ether (20 ml × 3) and the combined extracts were washed with saturated aqueous sodium chloride (10 ml) and dried (Na_2SO_4). Removal of solvent afforded an oil which was purified by flash chromatography [ether–light petroleum (3:7)] to give the epoxide (**17**) (81 mg, 76%), m.p. 85—88 °C not depressed by mixture with a sample prepared by method (i); $\nu_{max.}$ 3 130, 1 670, 1 550, 1 155, 1 055, and 980 cm^{-1}; δ_H (100 MHz) 0.90 and 1.00 (6 H, 2 × s, 2 × CH_3), 1.2—1.9 (7 H), 2.30 (2 H, m, oxirane CH_2), 2.5 (2 H, m, CH_2 CO), 6.75 (1 H, m, furan 4-H), 7.40 (1 H, m, furan 5-H), and 8.05 (1 H, m, furan 2-H); *m/z* 248 (M^+, 1), 139 (11), 123 (18), 95 (100), 81 (34), 69 (46), 55 (42), and 53 (41).

(±)-(αRS,3′SR,4′RS)-α-(3-*Furyl*)-5,5-*dimethyl*-1-*oxaspiro*-[2.5]*octane*-4-*ethanol* (**18**) *and* (±)-(αRS,3′RS,4′SR)-α-(3-*furyl*)-5,5-*dimethyl*-1-*oxaspiro*[2.5]*octane*-4-*ethanol* (**19**).—(i) Lithium aluminium hydride (1.1 mmol; 0.5M in THF) was added to a solution of the ketone (**17**) (1.0 g, 4 mmol) in THF (10 ml) at 0 °C. After 1 h water (0.5 ml) was added and the slurry was evaporated to dryness under reduced pressure. The solids were extracted with ether (10 ml × 5). Removal of solvent and chromatography of the residue on silica gel with ether–pentane (3:2) as eluant afforded the alcohols (**19**) (170 mg, 17%) and (**18**) (520 mg, 52%) in order of elution as oils which were used without further purification.

(ii) Lithium triethylborohydride (1.5 mmol; 1M in THF) was added to a stirred solution of the ketone (**17**) (340 mg, 1.4 mmol) in THF (10 ml) at −50 °C. After 30 min at −50 °C the mixture was quenched by the addition of 10% aqueous sodium hydroxide (2 ml) and allowed to warm to room temperature. Extraction of the products with ether (20 ml × 3) and chromatography of the extract as described above gave the alcohols (**19**) (173 mg, 51%) and (**18**) (71 mg, 21%) as oils which were used without further purification. Compound (**18**) had $\nu_{max.}$ 3 200—3 600, 2 900, 1 455, 1 360, 1 100, 1 050, and 780 cm^{-1}; δ_H (100 MHz) 0.98 and 1.02, (6 H, 2 × s, 2 × CH_3), 1.1—2.1 (9 H), 2.82 (2 H, br s, oxirane CH_2), 4.64 (1 H, m, C*H*OH), 6.42 (1 H, br s, furan β-H), and 7.40 (2 H, br s, furan α-H); *m/z* 250 (M^+, 4) 232 (2), 219 (17), 111 (80), 110 (66), 97 (85), 95 (71), 81 (68), 69 (100), and 55 (61) [Found (h.r.m.s.): M^+ 250.1579. Calc. for $C_{15}H_{22}O_3$: *M*, 250.1567]; compound (**19**) had $\nu_{max.}$ 3 200—3 600, 2 900, 1 455, 1 355, 1 100, 1 050, and 775 cm^{-1}; δ_H (100 MHz) 0.90 and 1.06 (6 H, 2 × s, 2 × CH_3), 1.2—2.1 (9 H), 2.72 (2 H, s, oxirane CH_2), 4.94 (1 H, m, C*H*OH), 6.42 (1 H, br s, furan β-H), and 7.40 (2 H, br s, furan α-H); *m/z* 250 (M^+, 2), 232 (7), 219 (17), 111 (77), 110

(100), 97 (66), 95 (73), 81 (56), and 69 (69); [Found: (h.r.m.s.) M^+, 250.1571]

(±)-(αRS,1'RS,2'RS)-α-[(2'-*Hydroxy*-2',6',6',6'-*trimethylcyclohexyl*)*methyl*]*furan*-3-*methanol* (**10**) *and* (±)-(αRS,1'RS,2'SR)-α-[(2'-*Hydroxy*-2',6',6'-*trimethylcyclohexyl*)*methyl*]*furan*-3-*methanol* (**14**).—Lithium aluminium hydride (20 mg) was added to a stirred solution of the epoxide (**18**) (70 mg, 0.28 mmol) in dry THF (10 ml) and the mixture was heated under reflux for 2 h. After the mixture had cooled to 0 °C, water (0.5 ml) was added and the mixture was filtered through Celite. The filtrate was evaporated to dryness under reduced pressure. The residue was purified by flash chromatography [ether–hexanes (4:1)] to give the diol (**10**) (48 mg, 69%) as a white, amorphous solid, m.p. 142—145 °C, identical with that prepared previously. In a similar manner the epoxide (**19**) (70 mg) yielded the diol (**14**) (43 mg, 61%) as a white amorphous solid, m.p. 140—142 °C, identical with that prepared previously.

trans-*Octahydro*-4,4,7a-*trimethylbenzofuran*-2-*ol* (**22**).—To a solution of the lactone (**23**) (230 mg, 1.3 mmol) in dry toluene (10 ml) at −78 °C was added di-isobutylaluminium hydride (1.4 mmol; 1.5M in toluene). After 1 h at −78 °C the mixture was treated with methanol (1 ml) and allowed to warm to room temperature. Saturated aqueous sodium chloride (2 ml) was added and the mixture was extracted with ether (10 ml × 4). The combined extracts were dried (Na_2SO_4) and evaporated under reduced pressure to leave a residue which was purified by flash chromatography [ether–pentane (1:1)] to afford the hemiacetal (**22**)[14] (180 mg, 77%) as an oil, which was used without further purification; $\nu_{max.}$ 3 200—3 600, 2 940, 1 725, 1 460, 1 375, 1 150, 1 080, and 965 cm^{-1}; δ_H (100 MHz) (*inter alia*) 0.82, 0.87, 0.95, 1.07, 1.15, and 1.30 (18 H, 6 × s, 6 × CH_3), 5.5 (0.75 H, t, *J* 7 Hz, C*H*OH), and 9.75 (0.25 H, t, *J* 3 Hz, C*H*OH); $\delta_H(CCl_4)$ (*inter alia*) 0.90, 1.00, 1.15 (3 H, s), and 5.45 (1 H, t, *J* 7 Hz); *m/z* 169 (59), 166 (7), 151 (24), 141 (22), 95 (60), 82 (73), 81 (57), 71 (100), and 43 (72).

(±)-(αRS,1'SR,2'SR)-α-[(2'-*Hydroxy*-2',6',6'-*trimethylcyclohexyl*)*methyl*]*furan*-3-*methanol* (**9**) *and* (±)-(αRS,1'RS,2'RS)-α-[(2'-*Hydroxy*-2',6',6'-*trimethylcyclohexyl*)*methyl*]*furan*-3-*methanol* (**13**).—A solution of the hemiacetal (**22**) (100 mg, 0.5 mmol) in THF (5 ml) was added to a stirred solution of 3-furyllithium [from 3-bromofuran (160 mg, 1.1 mmol) and n-butyllithium (1.1 mmol; 1.6M in hexane)] at −78 °C. The mixture was allowed to warm to −20 °C. Saturated aqueous ammonium choride (5 ml) was added and the slurry was allowed to warm to room temperature. The crude product was extracted into ether (10 ml × 4), the extracts were dried (Na_2SO_4), and the volatiles removed under reduced pressure. The residue was purified by flash chromatography [ether–pentane (65:35)] to give a mixture of the diols (**9**) and (**13**) as a white solid (97 mg, 71%) m.p. 54—59 °C. Integration of the furanyl methine resonances in the ^1H n.m.r. spectrum enabled the ratio of compounds (**9**) and (**13**) to be estimated as 3:1.

(±)-1-(3-*Furyl*)-(2α-*hydroxy*-2,6,6-*trimethylcyclohexyl*)-*ethanone* (**24**).—(i) To a stirred solution of the diols (**9**) and (**13**) (20 mg, 0.079 mmol) in dry methylene dichloride (10 ml) was added activated manganese(IV) oxide (0.07 g, 0.79 mmol). The resulting mixture was then stirred at room temperature for 4 h, filtered, and the solvent was removed under reduced pressure to leave a white crystalline solid which was purified by flash chromatography (40% ethyl acetate–light petroleum) as eluant to give exclusively the ketone (**24**) (18 mg, 90%), m.p. 77—78 °C; $\nu_{max.}$ 3 420m, 3 010—2 780s, 1 670s, 1 560m, 1 485m, 1 360w, and 1 255s cm^{-1}; δ_H (100 MHz) 8.05 (1 H, s, furan), 7.38 (1 H, m, furan), 6.71 (1 H, m, furan), 2.78 (2 H, m, CH_2CO), 2.08 (1 H, m, CH), 1.78—1.20 (6 H, m, 3 × CH_2), 1.08 (3 H, s, *trans*-fused CH_3), and 0.82 (6 H, s, 2 × *gem*-CH_3); *m/z* = 234 (8), 149 (10), 138 (17), 123 (37), 110 (100), 109 (75), 97 (44), 82 (86), 69 (50), and 43 (36); (h.r.m.s.) M^+, 250.1658 ($C_{15}H_{22}O_3$ requires *M*, 250.1569).

(ii) To a solution of 3-bromofuran (0.39 g, 2.64 mmol) in THF (5 ml) at −78 °C was added BuLi (1.8 ml, 2.64 mmol) and the reaction mixture was stirred at −78 °C for 30 min. A solution of the lactone (**23**) (60 mg, 0.33 mmol) in THF (5 ml) was then added dropwise, the cooling bath was removed, and the solution was allowed to warm to room temperature overnight. The resulting mixture was poured into water (15 ml), extracted with ether (4 × 20 ml), and the extract was washed with brine (50 ml) and dried over anhydrous potassium carbonate. Removal of solvent followed by purification by flash chromatography yielded the ketone (**24**) as a white crystalline solid (50 mg, 61%). The spectral and chromatographic characteristics of the isolated product (**24**) were identical with those previously reported.

(±)-(αRS,1'RS,2'RS)-α-[(2'-Hydroxy-2',6',6'-*trimethylcyclohexyl*)*methyl*]*furan*-3-*methanol* (**13**).—The ketone (**24**) (38 mg, 0.152 mmol) was dissolved in dry THF (10 ml) and the solution was cooled to −78 °C under nitrogen. A 1M solution of lithium triethylborohydride (32 mg, 0.030 mmol) in THF was added dropwise and the reaction mixture was stirred at −78 °C for 2.5 h and then allowed to warm slowly to room temperature overnight. Water (10 ml) was added and the resulting mixture was extracted with ether (3 × 20 ml), and the extract was washed with brine (30 ml) and dried over anhydrous potassium carbonate. Evaporation of the solvent yielded a white powder which was recrystallised from ether to give compound (**13**) as a white crystalline solid (36 mg, 94%), m.p. 85—87 °C, identical with that prepared previously.

(±)-(2α,3aβ,7aα)-2-(3-*Furyl*)*octahydro*-4,4,7a-*trimethylbenzofuran* [(±)-*Ancistrofuran*] (**2**).—The diol (**13**) (19 mg, 0.076 mmol) was taken up in dry pyridine (5 ml) and toluene-*p*-sulphonyl chloride (21 mg, 0.11 mmol) was added. After 40 h the mixture was poured into 0.5M-hydrochloric acid (10 ml) and extracted with ether (10 ml × 3). The extracts were washed with 0.1M-hydrochloric acid (5 ml × 2) and dried ($MgSO_4$). Removal of solvent afforded an oily residue which was purified by flash chromatography [ether–pentane (3:97) as eluant] to give (±)-ancistrofuran (**2**) (14 mg, 80%) as an oil, which decomposed on attempted distillation; $\nu_{max.}$ (CCl_4) 2 950, 1 500, 1 480, 1 160, 1 025, 990, 910, and 870 cm^{-1}; δ_H (100 MHz) 0.98, 1.00, and 1.14 (9 H, 3 × s, 3 × CH_3), 1.2—2.0 (8 H, 4 × CH_2), 2.1—2.4 (1 H, m, 3a-H), 4.96 (1 H, m, 2-H), 6.38 (1 H, br s, furan β-H), and 7.38 (2 H, br s, furan α-H); *m/z* 234 (M^+, 11), 220 (15), 219 (100), 191 (26), 149 (11), 138 (44), 123 (53), 109 (39), and 95 (65) [Found: (h.r.m.s.) M^+, 234.1623. $C_{15}H_{22}O_2$ requires *M*, 234.1618], identical with the natural product.

(±)-(2α,3aα,7aβ)-2-(3-*Furyl*)*octahydro*-4,4,7a-*trimethylbenzofuran* (**11**).—Diol (**9**) (10 mg, 0.04 mmol) was stirred with toluene-*p*-sulphonyl chloride (15 mg, 0.08 mmol) in pyridine (5 ml) for 24 h. Hydrochloric acid (0.5M; 1 ml) was added and the mixture was extracted with ether. The extracts were washed with 0.1M-hydrochloric acid (2 ml × 2), dried ($MgSO_4$), and the volatiles were removed under reduced pressure. The residue was purified by passage through a short plug of silica gel with ether–pentane (4:96) as eluant to yield the cyclic ether (**11**) (4.1 mg, 44%) as an oil which was not purified further. Using this procedure diol (**10**) (25 mg) afforded the cyclic ether (**12**) (11.4 mg, 49%) and diol (**14**) (25 mg) furnished the cyclic ether (**15**) (9.8 mg, 42%). The products were obtained as oils which were not purified further; (±)-(2α,3aα,7aβ)-2-(3-furyl)octahydro-4,4,7a-trimethylbenzofuran (**11**) had $\nu_{max.}$(CCl_4) 2 950, 1 500,

1 475, 1 460, 1 380, 1 160, 1 100, 1 080, 1 025, and 990 cm^{-1}; δ_H (100 MHz) 0.88, 0.94, and 1.20 (9 H, 3 × s, 3 × CH_3), 1.4—2.3 (9 H), 5.06 (1 H, dd, *J* 8 and 3 Hz, 2-H), 6.36 (1 H, br s, furan β-H), and 7.38 (2 H, m, furan α-H); *m/z* 234 (M^+, 11), 219 (22), 138 (68), 123 (69), 109 (28), 95 (86), 82 (100), 69 (66), and 68 (65); (±)-(2α,3aα,7aα)-2-(3-furyl)octahydro-4,4,7a-trimethylbenzofuran (**12**) had $\nu_{max.}$(CCl_4) 2 950, 1 500, 1 475, 1 160, 1 020, 990, and 905 cm^{-1}; δ_H (100 MHz) 0.90, 1.05, and 1.42 (9 H, 3 × s, 3 × CH_3), 1.2—2.4 (9 H), 4.90 (1 H, dd, *J* 7 and 3 Hz, 2-H), 6.34 (1 H, br s, furan β-H), and 7.34 (2 H, br s, furan α-H); *m/z* 234 (M^+, 19), 219 (71), 191 (100), 149 (19), 123 (30), 109 (22), 95 (29), and 82 (36) [Found: (h.r.m.s.) M^+, 234.1607. $C_{15}H_{22}O_2$ requires *M*, 234.1618]; (±)-(2α,3aβ,7aβ)-2-(3-furyl)octahydro-4,4,7a-trimethylbenzofuran (**15**) had $\nu_{max.}$(CCl_4) 2 950, 1 505, 1 480, 1 025, 990, and 875 cm^{-1}; δ_H (100 MHz) 0.95, 1.00, and 1.41 (9 H, 3 × s, 3 × CH_3), 1.2—2.4 (9 H), 4.94 (1 H, m, 2-H), 6.35 (1 H, br s, furan β-H), and 7.37 (1 H, br s, furan α-H); *m/z* 234 (34), 219 (57), 192 (11), 191 (100), 149 (22), 123 (46), 109 (30), and 95 (48) [Found: (h.r.m.s.) M^+, 234.1611. $C_{15}H_{22}O_2$ requires *M*, 234.1618].

References

1 R. Baker and S. Walmsley, *Tetrahedron*, 1982, **38**, 1899; G. D. Prestwich, *J. Chem. Ecol.*, 1979, **5**, 459; *Ann. Rev. Entomol.*, 1984, **29**, 201.
2 B. P. Moore, *J. Insect Physiol.*, 1968, **14**, 33.
3 J. Vrkoe and K. Ubik, *Tetrahedron Lett.*, 1974, 1463.
4 A. Quennedey, G. Brulé, J. Rigaud, P. Dubois, and R. Brossut, *Insect Biochem.*, 1973, **3**, 67; G. D. Prestwich, M. Kaib, W. F. Wood, and J. Meinwald, *Tetrahedron Lett.*, 1975, 4701; S. G. Spanton and G. D. Prestwich, *Tetrahedron*, 1982, **38**, 1921; G. D. Prestwich and M. S. Collins, *J. Chem. Ecol.*, 1981, **8**, 147.
5 G. D. Prestwich, *Tetrahedron*, 1982, **38**, 1911.
6 G. D. Prestwich and M. S. Collins, *Tetrahedron Lett.*, 1981, **22**, 4587.
7 R. Baker, H. R. Coles, M. Edwards, D. A. Evans, P. E. Howse, and S. Walmsley, *J. Chem. Ecol.*, 1981, **7**, 135.
8 G. D. Prestwich, D. F. Weimer, J. Meinwald, and J. Clardy, *J. Am. Chem. Soc.*, 1978, **100**, 2560; D. F. Weimer, J. Meinwald, G. D. Prestwich, B. A. Solheim, and J. Clardy, *J. Org. Chem.*, 1980, **45**, 191.
9 L. J. Wadhams, R. Baker, and P. E. Howse, *Tetrahedron Lett.*, 1974, 1697; R. Baker, D. A. Evans and P. G. McDowell, *J. Chem. Soc., Chem. Commun.*, 1977, 111.
10 R. Baker, D. A. Evans, and P. G. McDowell, *Tetrahedron Lett.*, 1978, 4073.
11 Y. Naya, G. D. Prestwich, and S. G. Spanton, *Tetrahedron Lett.*, 1982, **23**, 3047.
12 R. Baker, P. H. Briner, and D. A. Evans, *J. Chem. Soc., Chem. Commun.*, 1978, 410.
13 R. Baker, P. H. Briner, and D. A. Evans, *J. Chem. Soc., Chem. Commun.*, 1978, 981.
14 T. R. Hoye and A. J. Caruso, *J. Org. Chem.*, 1981, **46**, 1198.
15 O. P. Vig, M. L. Sharma, N. Trehan, and N. K. Verma, *Indian J. Chem., Sect. B*, 1980, **19**, 450.
16 M. Parilli, M. Adinolfi, G. Barone, G. Laonigro, and L. Mangoni, *Gazz. Chim. Ital.*, 1975, **105**, 1301.
17 T. R. Hoye and M. J. Kurth, *J. Org. Chem.*, 1979, **44**, 3461.
18 M. T. Reetz, K. Kesseler, and A. Jung, *Tetrahedron Lett.*, 1984, **25**, 728.
19 T. Nakata, M. Fukui, M. Ohtsuka, and T. Oishi, *Tetrahedron Lett.*, 1983, **24**, 2661.
20 T. Fukuyama, B. Vranesic, D. P. Negri, and Y. Kishi, *Tetrahedron Lett.*, 1978, 2741.
21 D. B. Collum, J. H. McDonald, and W. C. Still, *J. Am. Chem. Soc.*, 1980, **102**, 2118.
22 J. A. Scheider and W. C. Still, *Tetrahedron Lett.*, 1980, **21**, 1035.
23 W. C. Still, M. Kahn, and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923.

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